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**Introduction**

Cardiovascular disease isfescalating in recent years andgremains as a leading cause of mortality in developing countries (1). It is can occur during the therapy with several cytotoxic drugs, including 5- fluorouracil and may be the dose limiting factor in cancer treatment and hence tumor response (2). Cardiac toxicity includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to cardiomyopathy. In literature, different mechanisms of chemotherapy induced cardiac toxicity are postulated including cellular damage due to the formation of free oxygenjradicals and the induction ofnimmunogenic reactions with thedpresence of antigen presenting cells in the heart. Moreover, the influence of the cytotoxic agents on certain phospholipids, especially cardiolipin, may also explain the development of cardiac toxicity (2).

5- Fluorouracil (5-FU) is an antimetabolite thatfacts during the S phase of the cell cycle and is activated by thymidinefphosphorylase into fluorodeoxyuridylate (5 fluoro 2'deoxyuridine 5'monophosphate, 5-FdUMP) that inhibitsdthymidylate synthase, thus preventing DNAgsynthesis that leads to imbalanced cellfgrowth and ultimately cell death (3-5 ). It is a potentdantineoplastic agent commonly used for treatment of various malignanciesfincluding gastrointestinal, breast and head and neck cancer. In addition to bonevmarrow depression, gastrointestinal tract reaction, or even leucopenia anddthrombocytopenia (6), it has diverse adverse effects such as cardiac toxicity, hepatotoxicity and nephrotoxicity which restrict its wide and extensive clinical usage, also it causes marked organ toxicity coupled with increased oxidative stress and apoptosis (7).

Medicinal plants and theirdderivatives are widely used all over the world as medicinal, salutistic or functional food. Some medicinalfplants are promising natural source (8). Artichoke (*Cynara scolymus L*.) is one of the world’s oldest medicinal plants. It is anfimportant crop of ancient Greece, grows in Egypt, Mediterranean area and other countries .It is belonging to the family (Asteraceae) (9). It has medical properties and used in traditional folk medicine mainly because of theirfcholeretic (increasing bile secreation), diuretic and hypocholesterolemic activities (10). It is a good source of natural antioxidants such as vitamin C, hydroxycinnamic acids (9) and caffeoylquinic acid derivatives (cynarin and chlorogenic acid) (11). Artichoke plant is rich with flavonoids (luteolin, apigenin), which its potential protectiveveffect as antioxidant have been demonstrated for the extracts of this vegetable indreducing reactive oxygen species (ROS) from stimulated human neutrophilfand in protection of hepatocyte from t-butyl hydrogen peroxide inducedfcytotoxicity (12). The artichoke extracts were assessed for their protective role in the control of oxidative damagefto biological molecules (proteins, lipids and DNA), caused by free radicals such as RCOO and/or OH, using the b- potential antioxidant effect. Several *in vitro* studies have showndthat the antioxidant potential effect of ALE is

dependent on radicaldscavenging and metal ion chelating effectfof its constituents such as cynarin, chlorogenic acid and flavonoids. Pure constituents of ALE have also been shown to produce less inhibitory activity on free radical production than the extract itself (13).

**Materials and Methods**

***Chemicals and Drugs***

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5-Fluorouracil (5-FU) obtained from EBEWE pharma, AUSTRIA. Dimethyl sulfoxide (DMSO) and ethanol solvent obtained from warehouse chemicals of College of Pharmacy/ University of Baghdad.

***Reagents***

Standard assay rat’s kits for AST/GOT and ALT/GPT were obtained from Egyption Company For Biotechnology (S.A.E) and for CK obtained from Biolabo SA, 02160 ,Maizy, France.

***Plant materials***

The plant was collected from the Garden of Medicinal Plants at the Department of Pharmacognosy and Medicinal plants / College of Pharmacy / University of Baghdad. The leaves of the plant were dried in shade at room temperature, then rendered into a fine powder by using electrical mill and weighed.

***Extraction of the plant***

Four grams of powdered leaves were extracted by maceration with 2500 ml of absolute ethanol for one week, then the extract was filtered and evaporated to dryness under reduced pressure by using rotary evaporator, after that the collected amount was weighted (14).

***Preparation of the extract for injection***

A specific weights (4.5 gm.) from the dried ethanolic artichoke extract was dissolved in dimethyl sulfoxide (112.5 ml) to get a concentration of 40 mg/ml (as a stock solution) (13).

***Experimental animals***

Twenty -four female albino rats of 1-2 month old (average body weight 150-200gm), were obtained from animal house of the college of pharmacy/ university of Baghdad. The animals were acclimatized under standard laboratory conditions for 2 weeks prior to treatment .They had free access to standard diet and water. They were maintained under standard condition of temperature (30ºC), humidity and light / dark cycles. All the experimental studies were conducted inconformity with the guidance for care and standard experimental animals of our College ethical protocol. The animals were used in this study divided equally into four groups, each group with 6 rats they were treated as following: Group I: (negative control) received oral daily dose of DMSO (2 ml/kg /day) for 10 successive days. Group II: (positivecontrol), received oral daily dose of DMSO (2 ml/kg /day) for 10 successive days with administered single dose of 5-FU (150 mg/kg) intraperitoneally on 8th day (7) in association with DMSO. Group III: received 200 mg/kg/day (13) of ethanolic artichoke extract orally for 10 successive days. Groups IV: received 200 mg/kg/day (13) of ethanolic artichoke extract orally 10 successive days with subsequently single intraperitoneal dose of 5-FU (150 mg/kg) on 8th d (7) in association with the ethanolic artichoke extract (13).After 24 h of the end of the experimental period (10 days), all the animals were anesthetized under light diethyl ether anesthesia and blood samples were collected in clean test tubes by intracardiac puncturing and allowed to clot at room temperature.

***Biochemical assessment***

The serum was separated by centrifugation for 20 min at 3600 round per minute (r.p.m.) and stored into eppendorff tubes at – 20 °C to be used for determination of creatine Kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (13).

**Results and Discussion**

Data were subjected to statistical analysis, data were expressed as the mean values mean± standard deviation (SD) of samples. The Statistical significance of the differences between various groups was determined by student unpaired t- test. Differences were considered statically significant for p-value < 0.05.

***The effects of ethanolic artichoke extract on 5-fluorouracil (5-FU) induced cardiac-toxicity in rats:***

5-FU (Group ΙΙ) significantly (P<0.05) increased serum levels of AST, ALT, and CK with respect to Group Ι. Administration of ethanolic artichoke extract in association with 5-FU (Group IѴ) significantly (P<0.05) decreases the serum levels of AST, ALT and CK with respect to Group ΙΙ. Groups ΙΙΙ show no significant differences (P<0.05) in ALT and CK with respect to Group Ι, but there was significant difference in AST with respect to group I. While group IV showed significant elevation (P<0.05) in AST, ALT and CK with respect to Group Ι, as shown in Table (1).

Cardiac toxicity is one of the dangerous side effect of 5-FU , which often presents as myocardial ischemia, but to a lesser extent cardiac arrhythmia, hyper and hypotension, left ventricular dysfunction, cardiac arrest and sudden death (15-20). The incidence of 5-FU induced cardiac toxicity varies between 0-35 % and this may depend on dose, cardiac comorbidity and schedule of chemotherapy (15, 16, 18). The clinical handling of 5-FU-induced cardiac toxicity is difficult as the pathophysiological mechanisms underlying this cardiac toxicity remain undefined (15, 21). However several mechanisms havebbeen proposed, including vascular endothelial damage followed by coagulation, ischemia secondary to coronary artery spasm, direct toxicity on the myocardium andfthrombogenicity due to altered rheological factors (21).

The pathogenesis of 5-FU induced cardiac toxicity may involve oxidative stress with increased levels of superoxide anion after 5-FU treatment (22).The activities of superoxide dismutase (SOD) and glutathion peroxidase (GSH-Px) were lowered in 5-FU treated guinea pigs (23) demonstrating a reduced antioxidant capacity. If not eliminated by cellular antioxidant systems, superoxide anions can generate the highly reactive and toxic hydroxyl radicals through the Haber–Weiss reaction, which is catalyzed by iron (24,25). Increased reactive oxygen species (ROS) levels inside cells lead to oxidation of macromolecules, including lipids, nucleic acids, and proteins, thereby disturbing cellular functions (25). In addition to ROS, pro-inflammatory cytokines, such as tumourdnecrosis factor- α (TNF-α) and interleukins (IL)-1 and 6, also play an indirectdrole in production toxicity and organs damage that generate by chemotherapy agents, as 5-FU (26).

The present study confirms the cardiac toxicity of 5-FU, as evidenced by the significantly (P<0.05) elevation in serum level of AST, ALT and CK. Detection of elevated concentrations of cardiac biomarkers in blood is a sign of cardiac injury which could be due to supply–demand imbalance, toxic effects, or haemodynamic stress (27). Creatine kinase (CK), AST, lactate dehydrogenase, myoglobin, and troponins are some of these markers (28).

The present study hasdshown a successful reduction in cardiac toxicity induced by 5-FU in albino rats after treatment with ethanolic artichoke extract, this was reflected by reduction in serum level of AST, ALT and CK. This is give a strongly refers to the possible cardiac protective effects of artichoke extract against 5-FU induced cardiac toxicity in the rats. This protective effect of artichoke extract related to the power antioxidant effect of phenolic acids especially chlorogenic acid and cyanine (29) .When the biological activity of artichoke extracts is considered, the presence of luteolin-7- glucoside and hydrolysable tannins, besides caffeoylquinic derivatives, in the phenolic fractionfof these extracts must be taken into account: all these phenolics possess a good antioxidantfactivityfagainst peroxyl and hydroxyl radicals by decreasing the release of ROS, which is produced by effect of cytotoxic drugs, when assessed using the beta- carotene/linoleate assay and the metmyoglobin assay (30).

**Table (1) Effects of ethanolic artichoke extract (200 mg/kg) on the serum levels of AST, ALT and CK in albino female rats with 5-FU induced cardiac toxicity, data are expressed as Mean ± SD, n =6,\* p <0.05. Standard deviation (SD), 5-Fluorouracil (5-FU) and dimethyl sulfoxide (DSMO).**

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| **Treatment group**  **n=6** | **Type of treatment** | **Serum** **Aspartate aminotransferase (S.AST)**  **Up to 40 IU/L**  **(Mean ± SD)** | **Serum Alanine aminotransferase (S.ALT)**  **Up to 40 IU/L**  **(Mean ± SD)** | **Serum Creatine kinase (S.CK)**  **Up to 190 IU/L**  **(Mean ± SD)** |
| I | Dimethyl sulfoxide (DMSO) only | 27.33 ± 0.42 | 7.33 ± 0.81 | 51.33 ± 4.35 |
| II | 5-Fluorouracil (5-FU) | 74.06 ± 11.52\* | 32.53 ± 1.43\* | 555.66 ± 67.77 \* |
| III | 200 mg/kg of Ethanolic artichoke extract | 22.33 ± 2.60 \* | 7.2 ± 4.73 | 48.42 ± 9.40 |
| IV | 200 mg/kg of Ethanolic artichoke extract + 5-FU | 31 ± 1.93 s | 16 ± 0.44 \*s | 63.6 ± 5.05 \*s |

(\*): Significant difference with respect to negative control group (P< 0.05), (s): Significant difference with respect to 5-FU treated group.

**Conclusion**

The results of this study suggested that the ethanolic artichoke extract has protective effects against 5-FU-induced cardiac toxicity in albino female rats. However, before a conclusive statement can be made on the potential antioxidant activity of artichoke extract as an adjunct to 5-FU therapy, there is a need for further long-term chronic studies for different fractions of artichoke extracts.

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